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RADIATION RESEARCH 121, 84–90 (1990)

Involvement of Prostaglandins and Histamine in Radiation-Induced Temperature Responses in Rats

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KANDASAMY, S. B., AND HUNT, W. A. Involvement of Prostaglandins and Histamine in Radiation-Induced Temperature Responses in Rats. *Radiat. Res.* 121, 84–90 (1990).

Exposure of rats to 1–15 Gy of γ radiation induced hyperthermia, whereas exposure to 20–150 Gy produced hypothermia. Since radiation exposure induced the release of prostaglandins (PGs) and histamine, the role of PGs and histamine in radiation-induced temperature changes was examined. Radiation-induced hyper- and hypothermia were antagonized by pretreatment with indomethacin, a cyclooxygenase inhibitor. Intracerebroventricular administration of PGE2 and PGD2 induced hyper- and hypothermia, respectively. Administration of SC-19220, a specific PGE2 antagonist, attenuated PGE2- and radiation-induced hyperthermia, but it did not antagonize PGD2- or radiation-induced hypothermia. Consistent with an apparent role of histamine in hypothermia, administration of disodium cromoglycate (a mast cell stabilizer), mepyramine (H1-receptor antagonist), or cimetidine (H2-receptor antagonist) attenuated PGD2- and radiation-induced hypothermia. These results suggest that radiation-induced hyperthermia is mediated via PGE2 and that radiation-induced hypothermia is mediated by another PG, possibly PGD2, via histamine.

INTRODUCTION

Exposure to ionizing radiation has been reported to induce hyperthermia in cats, rabbits, and humans (*1, 2*), hypothermia in guinea pigs (*3*), a biphasic response in monkeys (a fall followed by a rise) (*4*), and a dual effect in rats (low and high doses produced hyper- and hypothermia, respectively) (*5*). When rats were exposed to low doses of radiation either to the head or to the whole body, hyperthermia was observed, while body-only exposure induced no significant effect (*5*). This suggests that radiation-induced hyperthermia is a result of a direct action on the brain. Radiation-induced hyperthermia can also be attenuated by pre- or post-treatment with indomethacin, a cyclooxygenase inhibitor (*5*). Hyperthermia can also be reduced by the central administration of naloxone, a μ-receptor antagonist, but only after low doses of radiation (*5*). Taken together, these findings suggest that radiation-induced hyperthermia is mediated through the synthesis and release of prostaglandins (PGs) in the brain and to a lesser extent through the release of endogenous opioid peptides.

Radiation induces dramatic increases in the levels of prostaglandins in a variety of tissues (*6–10*) including brain (*11*). The E series of PGs have been identified in the brain as well as in the cerebrospinal fluid and have been suggested as a mediator of hyperthermia by Milton and co-workers (*12–15*), although Cranston *et al.* reported results contradicting this hypothesis (*16*). Several recent studies suggest that rodent brain contains predominantly PGD2 (*17–22*). Mast cells release histamine and also synthesize and subsequently release PGD2 as a major cyclooxygenase metabolite of arachidonic acid after activation by various stimuli (*23*). Histamine and PGD2 induce hypothermia and have been implicated in thermoregulation (*24–27*). In chickens, rabbits, and rats, central administration of histamine has a dual effect. After low doses hypothermia is observed. However, after high doses of histamine, hyperthermia is induced (*28–30*). In sheep, systemic injection of histamine also induced hyperthermia but only at warm ambient temperatures (*31*). Since exposure of rats to radiation-induced hyper- or hypothermia, depending on the dose, and the release of PGs and histamine (*5*), the role of PGs and histamine in radiation-induced temperature changes was investigated using inhibitors/antagonists of PGs and histamine. Also, it was determined whether or not high doses of radiation act on the brain or on peripheral sites.

METHODS

Drugs. The drugs used were PGE2, PGD2, and indomethacin (Sigma Chemical Co., St. Louis, MO); mepyramine maleate (Mallinckrodt Inc., St. Louis, MO); cimetidine (Smith Kline and French Laboratory, Philadelphia, PA); disodium cromoglycate (Fisons Corporation, Bedford, MA); 1-acetyl-2(8-chloro-10,11-dihydro-benz-[b,f]-[1,4]-oxazepine-10-carbonyl)hydrazine (SC-19220) (G. D. Searle Laboratory, Chicago, IL); ketamine hydrochloride (Parke-Davis, Detroit, MI); xylazine (Hayer Lockhart, Shawnee, KS); and acepromazine (Ayerst Laboratories, NY). Mepyramine and disodium cromoglycate were dissolved in sterile, nonpyrogenic saline. Cimetidine was dissolved in 0.1 ml of 1 *N* HCl and diluted to the final volume with saline. PGE2 and PGD2 were stored at −20°C and were dissolved in sterile saline before the injection. SC-19220 was dissolved in a mixture of 40% DMSO and saline.

Animals. Male Sprague–Dawley Crl:CD(SD)BRD rats (Charles River Breeding Laboratories, Kingston, NY) weighing 200–300 g were used in

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TABLE I
Changes in Rectal Temperature of Rats 15 Min after Exposure to Variable Doses of Ionizing Radiation

Dose (Gy)	Mean Δ temperature (°C)
Sham	+0.1 ± 0.05 (12)
1	+0.2 ± 0.05 (10)
3	+0.4 ± 0.10 (10)
5	+0.5 ± 0.05 (10)*
10	+0.9 ± 0.05 (10)*
15	+0.9 ± 0.10 (10)*
20	0.4 ± 0.05 (10)
50	0.8 ± 0.05 (10)*
100	0.9 ± 0.05 (10)*
150	1.2 ± 0.10 (10)*

* Significantly different from sham irradiation; $P < 0.05$. Values represent the mean ± SE. Numbers in parentheses are the number of animals in each group.

these experiments. Rats were quarantined on arrival and screened for evidence of disease by serology and histopathology before being released from quarantine. The rats were housed individually in polycarbonate isolator cages (Lab Products, Maywood, NJ) on autoclaved hardwood contact bedding ("Beta Chip" Northeastern Products Corp., Warrensburg, NY) and were provided commercial rodent chow ("Wayne Rodent Blok" Continental Grain Co., Chicago, IL) and acidified water (pH 2.5 using HCl) *ad libitum*. Animal holding rooms were kept at 21 ± 1°C with 50 ± 10% relative humidity on a 12-h, light:dark lighting cycle with no twilight.

Radiation exposure. Rats were placed in clear plastic well-ventilated containers for approximately 5 min before irradiation or sham exposure. The animals were then exposed bilaterally to varying doses of γ photons using a ^{60}Co source at a rate of 10 or 20 Gy/min. Lead bricks were used to shield the head (including the neck) or the body (thorax to pelvis). Each animal was placed in a plastic restraining tube that was enclosed in a cave made of lead bricks with a minimum thickness of 10 cm. The bricks were drilled to accept the part of the tube containing either the head or the body of the rat. During the irradiation, the rats were observed with a remote video monitor to verify that the animals did not shift position within the tube. Dosimetry was performed using an exposure-monitoring 50-cc ion chamber. Delivered dose was expressed as a ratio of the dose measured in a tissue-equivalent plastic phantom enclosed in a restraining tube to that measured in air.

Central administration of drugs. Rats were anesthetized with 1 ml/kg of a mixture of ketamine (50 mg/kg), xylazine (5 mg/kg), and acepromazine (1 mg/kg) given intramuscularly and were placed in a rat stereotaxic apparatus (David Kopf Instruments, No. 320). A single cannula was inserted into the lateral ventricle according to coordinates derived from the atlas of Pelligrino *et al.* (32): 0.8 mm posterior to bregma, 2.5 mm lateral. The cannula was lowered until cerebrospinal fluid rose in the cannula. Dental acrylic was used to secure the cannula. After the end of an experiment, injection sites were histologically verified. The volume of injection was always 10 μl. At least 1 week was allowed for recovery before animals were used for experiments. Injections/irradiations were performed at the same time of day (0900) to avoid diurnal variations in temperature. The antagonists (indomethacin, SC-19220, disodium cromoglycate, mepyramine, and cimetidine) were given 30 min before the administration of the radiation/prostaglandins.

Measurement of body temperature. All experiments were performed at an environmental temperature of 22 ± 1°C. The animals were placed in cages 1 h before the beginning of the experiments and body temperature was measured every 15 min over a period of 2 h with thermistor probes inserted approximately 6 cm into the rectum and connected to a datalogger (Minitrend 205). After each experiment, all animals were euthanized immediately with an overdose of carbon dioxide via inhalation.

Statistics. Statistical evaluations were undertaken using analysis of variance with a significance level of $P < 0.05$. Intergroup comparisons were performed using Tukey's test.

RESULTS

Exposure of rats to 1–15 Gy radiation induced hyperthermia, whereas exposure to 20–200 Gy induced hypothermia (Table I). The onset of these effects was rapid, and they reached their maximum response within 15 min. On the basis of these results, a dose of 10 Gy of radiation was used to study hyperthermia, and a dose of 50 Gy was chosen to study hypothermia.

As can be seen in Fig. 1, hypothermia induced by a 50-Gy dose of γ radiation occurred only after whole-body or head-only exposure, not when the head was shielded. These results are similar to those found after low doses of radiation (5). Since whole-body exposure resulted in the same effect as head-only exposure, subsequent studies used only whole-body exposure to ionizing radiation.

Experiments were undertaken to determine the effect of indomethacin, an inhibitor of prostaglandin synthesis, on radiation-induced changes in body temperature. Pretreatment with 1–5 mg/kg of indomethacin given intraperitoneally inhibited both the hyper- and hypothermia induced by exposure to 10 and 50 Gy of radiation, respectively (Fig. 2). Indomethacin alone had no effect on body temperature.

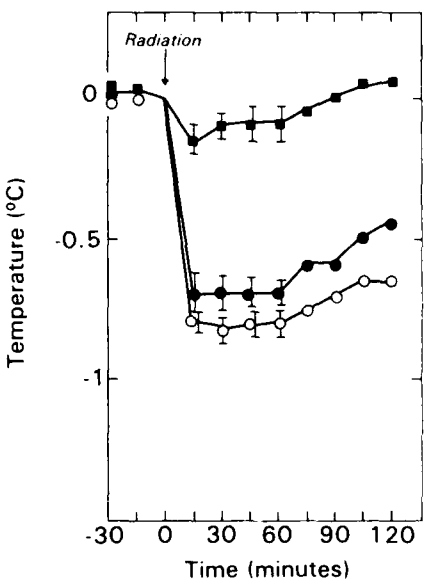

FIG. 1. Effects of 50 Gy of ionizing radiation on body temperature exposed body-only (■), whole-body (●), or head-only (○). Each point represents the mean ± SE of observation of six animals. Zero on the ordinate represents the temperature at the time of irradiation.

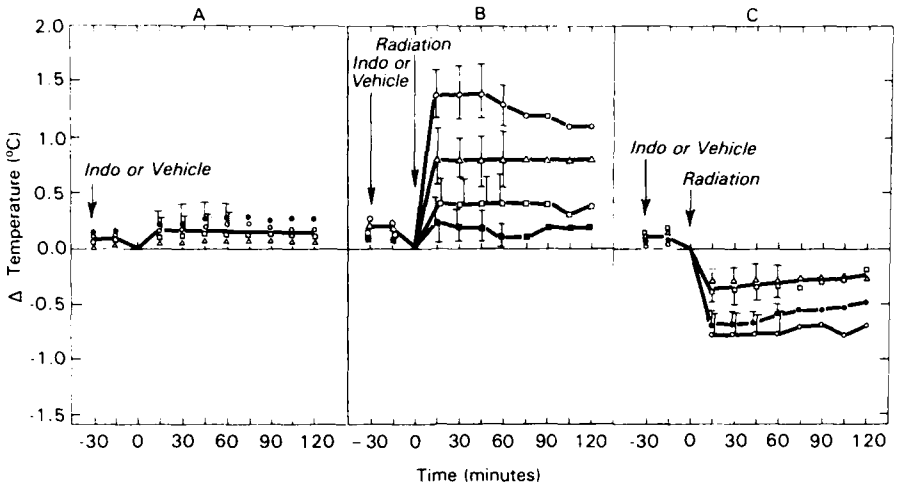

FIG. 2. Effect of indomethacin given ip (Indo) on hyper- and hypothermia induced by 10 and 50 Gy of radiation, respectively. (A) Nonirradiated controls given indomethacin, 1 (○), 3 (△), or 5 mg/kg (□), or vehicle (●); (B) 10 Gy of radiation alone (○) or in the presence of 1 (△), 3 (□), or 5 mg/kg (■) indomethacin; (C) 50 Gy of radiation alone (○) or in the presence of 1 (●), 3 (△), or 5 mg/kg (□) indomethacin. Each point represents the ±SE of observations on five animals. Zero on the ordinate represents the temperature at the time of second injection.

Similar to the effects of low and high doses of radiation, PGE2 (5–20 ng, icv) and PGD2 (10–15 ng, icv) produced dose-dependent hyper- and hypothermia (data not shown). Pretreatment with indomethacin, although it attenuated radiation-induced temperature responses, had no significant inhibitory effect on those of PGE2 or PGD2 (data not shown).

The effect of SC-19220, a PGE2 antagonist, was investigated on PGE2-, PGD2-, and radiation-induced temperature responses. Selected doses of SC-19220 (100–500 ng, icv), which had minimal effects on temperature in control animals, were given prior to PGE2 or PGD2 administration or to exposure to 10 or 50 Gy radiation. The SC-19220 significantly attenuated PGE2- (data not shown) or radiation-induced hyperthermia (Fig. 3) but had no effect on PGD2- (data not shown) or radiation-induced hypothermia (Fig. 3).

Since histamine stored in mast cells throughout the body (*25, 33*) is released by exposure to radiation (*34*), its possible role in thermoregulatory effects of radiation was examined. Disodium cromoglycate is known to be a potent inhibitor of the immunological release of chemical mediators secreted from mast cells (*35*). Disodium cromoglycate (100–500 ng, icv) attenuated PGD2- and radiation-induced hypothermia (Fig. 4).

To examine the role of histaminergic H1 and H2 receptors in PGD2-induced hypothermia, mepyramine (100–300 ng, icv), an H1 antagonist, or cimetidine (100–300 ng, icv), an H2 antagonist, was administered before irradiation. Previous results (5) have indicated that mepyramine and cimetidine are specific H1 and H2 receptor antagonists, respectively. Mepyramine antagonized hypothermia induced by 2-methyl histamine, an H1 agonist, but did not antagonize the hypothermia induced by 4-methyl histamine, an H2 agonist. Likewise, cimetidine significantly attenuated the hypothermia induced by 4-methyl histamine but not that induced by 2-methyl histamine. Both mepyramine and cimetidine, which are found to antagonize hypothermia induced by histamine (5), attenuated PGD2- and radiation-induced hypothermia (Figs. 5 and 6).

DISCUSSION

As reported earlier, ionizing radiation induced either hyper- or hypothermia in rats depending upon the dose (*5*), changes that appear to be centrally mediated. There are numerous reports that have demonstrated significant increases in PG levels in a variety of tissues including the brain after whole-body irradiation (*6–11*). The observations that PGs induce changes in body temperature and that various anti-inflammatory drugs block the synthesis of PGs in tissue (*24, 36, 37*) have implicated PGs in thermoregulation. Indomethacin attenuates the hyper- or hypothermia caused by low and high doses of ionizing radiation, indicating that this effect may be mediated by PGs. However, it has no antagonistic effect on exogenous administration of PGE2 and PGD2, confirming that it interferes only with PG synthesis. Of the various PGs, it has been reported that only the E series are potent as pyretic agents and that PGD2 is hypothermic (*24, 37*). The present results support these findings. In addition, based on studies using a variety of smooth muscle preparations (*38, 39*) and studies of PGE2-induced fever (*40, 41*), SC-19220, a specific PGE2 antagonist, antagonized only PGE2- and radiation-induced hyperthermia induced by low doses of ionizing radiation, suggesting that radiation-induced hyperthermia is mediated by PGE2.

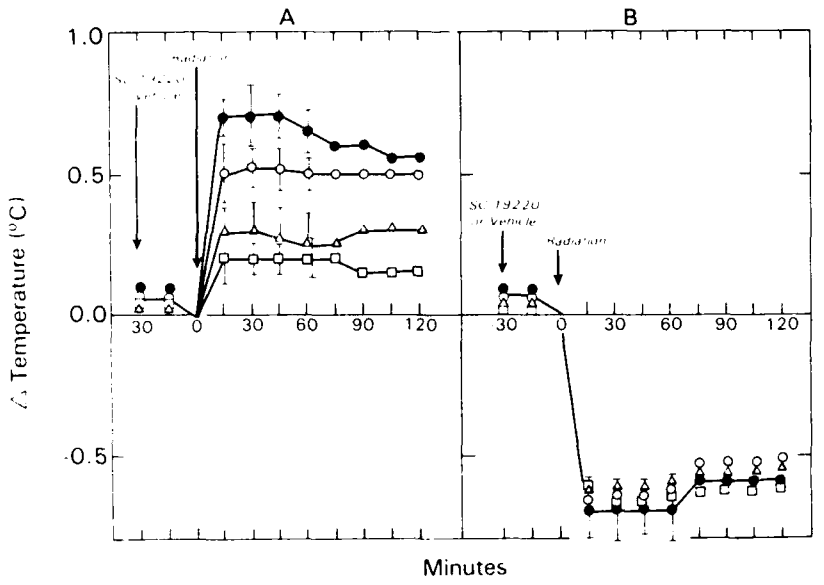

FIG. 3. Effect of SC-19220, icv, on hyper- and hypothermia induced by ionizing radiation. (A) 10 Gy irradiation alone (●) or in the presence of 100 (○), 300 (△), or 500 ng (□) SC-19220. (B) 50 Gy irradiation alone (●) or in the presence of 100 (○), 300 (△), or 500 ng (□) SC-19220. Each point represents the mean + SE of observations on five animals. Zero on the ordinate represents the temperature at the time of second injection.

Histamine has been implicated in the actions of ionizing radiation including hypotension, reduction in cerebral blood flow, and performance decrements (*42*). Furthermore, concentrations of histamine in circulating blood have been reported to be elevated in humans undergoing radiation therapy (*43*) as well as in dogs and monkeys (*34, 44, 45*) following radiation exposure. Tissue histamine levels are decreased in rats (*46*). Exposure to ionizing radiation resulted in hypothermia which appears to be mediated by the central release of histamine since the hypothermia occurred only after whole-body or head-only exposure, not when the head was shielded.

Histamine is present in high concentrations in the hypothalamus (*47, 48*) and is localized in nerve terminals (*49*), suggesting that it may act as a central neurotransmitter. Also, ascending histamine tracts are found in the median forebrain bundle (*50*); histidine decarboxylase, the enzyme that converts histidine to histamine, is localized in different regions of the brain (*51*); histamine activates adenylate cyclase in the brain (*52*); and brain histamine turnover is increased by stress (*53*). Administration of histidine systemically or histamine centrally evokes hypothermia caused by both H1- and H2-receptor activation (*54*). These neurochemical and pharmacological studies suggest that hista-

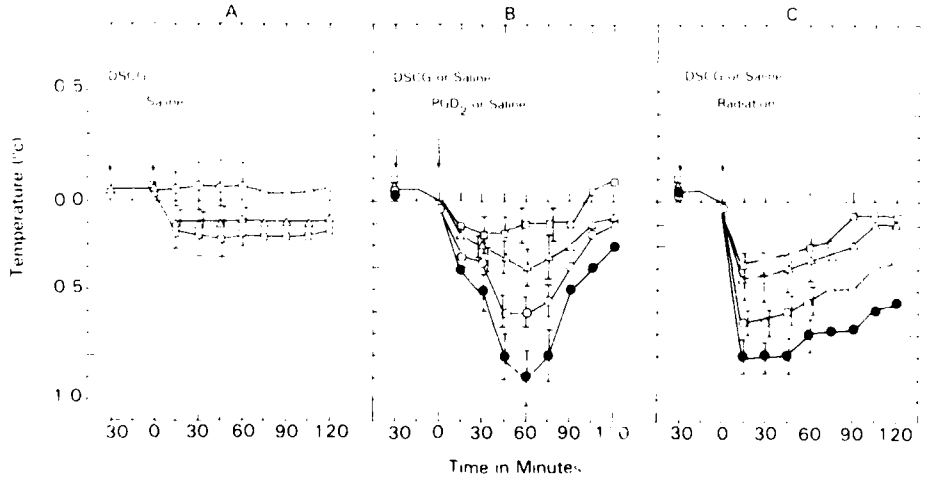

FIG. 4. Effect of disodium cromoglycate (DSCG), icv, on PGD2- and radiation-induced hypothermia. (A) Nonirradiated controls given 100 (○), 300 (△), or 500 ng (□) DSCG; (B) 30 ng of PGD2 alone (●) or in the presence of 100 (○), 300 (△), or 500 ng (□) DSCG; (C) 50 Gy irradiation alone (●) or in the presence of 100 (○), 300 (△), or 500 ng (□) DSCG. Each point represents the mean + SE of observations of five animals. Zero on the ordinate represents the temperature at the time of second injection.

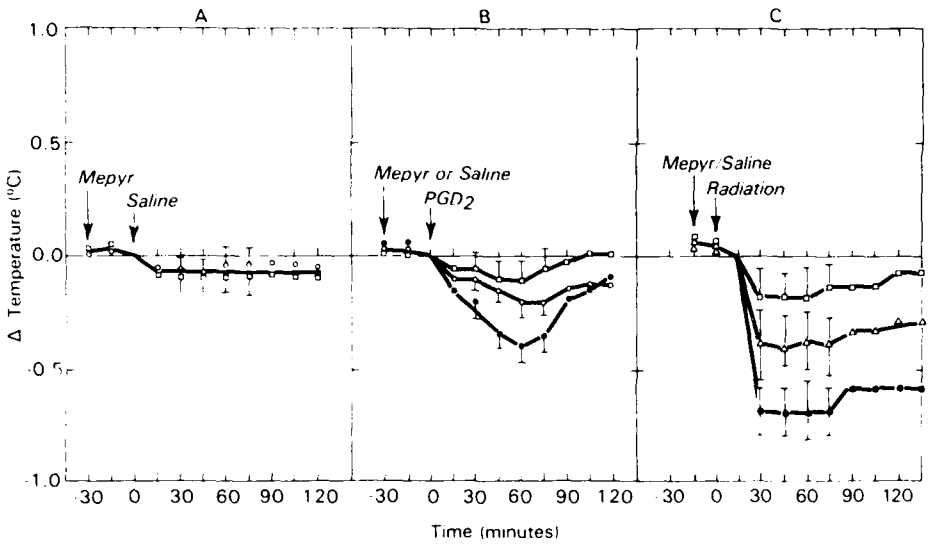

FIG. 5. Effect of mepyramine (Mepyr), icv, on hypothermia induced by PGD2 and ionizing radiation. (A) Nonirradiated controls given 100 (○) or 300 ng (□) mepyramine; (B) 30 ng of PGD2 alone (●) or in the presence of 100 (○) or 300 ng (□) mepyramine. (C) 50 Gy irradiation alone (●) or in the presence of 100 (△) or 300 ng (■) mepyramine. Each point represents the mean + SE of observations of five animals. Zero on the ordinate represents the temperature at the time of second injection.

mine may be a neurotransmitter involved in many physiological functions including thermoregulation and could underlie radiation-induced hypothermia.

Histamine is stored in mast cells throughout the body (*33*), including the brain, where they are particularly numerous in the hypothalamus (*55, 56*). Arachidonic acid is converted by the cyclooxygenase pathway primarily to PGD2 in mast cells in humans and rats (*17–22*). In addition, mast cells release PGD2 and histamine after activation by various stimuli (*23, 57*). It has been reported that PGD2 potentiates histamine-induced bronchoconstriction in man (*58*) and plasma extravasation in rat skin (*59*). In the present studies, the mast cell stabilizer disodium cromoglycate attenuated radiation- and PGD2-induced hypothermia, suggesting a role of central histamine in this response. The release of histamine acting on both H1 and H2 receptors

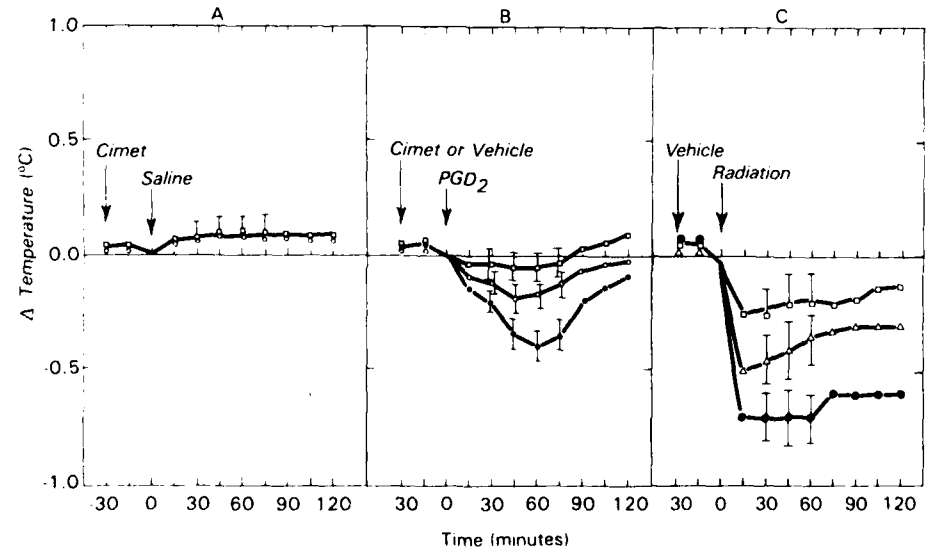

FIG. 6. Effect of cimetidine (Cimet), icv, on hypothermia induced by PGD2 and ionizing radiation. (A) Nonirradiated controls given 100 (○) or 300 ng (□) cimetidine; (B) 30 ng of PGD2 alone (●) or in the presence of 100 (○) or 300 ng (□) cimetidine; (C) 50 Gy irradiation alone (●) or in the presence of 100 ng (△) or 300 ng (■) cimetidine. Each point represents the mean + SE of observations of five animals. Zero on the ordinate represents the temperature at the time of second injection.

may be involved in radiation-induced hypothermia, since mepyramine, an H1-receptor antagonist, and cimetidine, an H2-antagonist, blocked not only radiation-induced hypothermia but also PGD2-induced hypothermia. Previous results have indicated that serotonin is not involved in radiation-induced hypothermia (5).

In summary, these results suggest that radiation-induced hyperthermia is mediated via PGE2, and histamine is involved in radiation-induced hypothermia. The attenuation of PGD2-induced hypothermia by disodium cromoblycate and antihistamines suggests that PGD2 acts via histaminergic systems.

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